IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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1623

In re Application of:	)	Group Art Unit: 1623
Chun-Ming Chen, Charles Carpenter, Haoyi Gu, Ali Naqui	)	Examiner: M. Moran
Serial No.: 08/942,369	)	Atty. Docket: 03604-0010-US00
Filed: October 2, 1997	)	
For: METHOD AND APPARATUS FOR CONCURRENTLY DETECTING PATHOGENIC ORGANISMS AND ANTIMICROBIAL SUSCEPTIBILITY	)	

APPELLANT'S BRIEF ON APPEAL
SUBMITTED PURSUANT TO 37 C.F.R. § 1.192

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicant hereby appeals the Examiner's final rejection mailed April 28, 1999 and pursuant to the Notice of Appeal filed October 14, 1999 hereby submits this Appeal Brief under 37 C.F.R. § 1.192. This brief is timely filed on or before April 14, 2000 with a four month extension of time.

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TABLE OF AUTHORITIES

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REAL PARTY IN INTEREST

IDEXX Laboratories, Inc. is the sole assignee of the above captioned patent application.

RELATED APPEALS AND INTERFERENCES

The Applicants are not aware of any pending matters before the Board of Patent Appeals and Interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF THE CLAIMS

Claims 20-24 and 26 are pending in the above captioned application (see Appendix). All other claims have been previously cancelled and the Examiner has indicated the amendments will be entered upon filing a Notice of Appeal and Appeal Brief (Advisory Actions of 6/14/99 and 7/22/99).

All pending claims are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of Johnson in view of Sanders and over Johnson in view of Sanders and further in view of Brocco. The Examiner also maintains that Edberg provides enablement for the claimed medium (Advisory Action mailed 10/25/99).

STATUS OF AMENDMENTS

Claims 1-11, 19, and 25 were cancelled in the Response mailed 7/8/99 without prejudice to further prosecution. The Examiner has indicated the amendments will be entered upon filing a Notice of Appeal and Appeal Brief (Advisory Actions of 6/14/99 and 7/22/99).

SUMMARY OF THE INVENTION

Bacterial urinary tract infections are one of the most common veterinary diseases. The primary causative agents of urinary tract infections are from the group of gram negative bacteria, more specifically the primary gram negative urinary pathogens. These typically will include, but are not limited to, E. coli, Klebsiella, Enterobacter and Proteus. Although the great majority of urinary tract infections (UTI) are caused by a single type of organism in the individual case, contaminating normal flora are often present on a patient's skin or fur or in the environment. Particularly in the veterinary context where the patient is an animal, collection of a urine specimen for analysis may often result in the specimen running along the patients skin or fur and being contaminated by the flora normally present there, or otherwise being collected in a non-sterile manner.

The present invention discloses methods of detecting the presence or absence of urinary pathogens in a biological sample and of simultaneously determining the susceptibility of the pathogens to various antimicrobial agents (p. 7, line 21 – p. 8, line 26). The present invention accomplishes this by providing a uropathogen specific medium, i.e., a medium which allows only the growth of the primary urinary gram negative pathogens and allows for substantially less growth of any other bacteria of a biological matrix (specification p. 12, line 11 et seq.; p. 19, Table 1). The specification defines the primary gram negative urinary pathogens as the group of bacteria which cause at least 85-90% of the human and veterinary urinary tract infections (specification, p. 10, line 19 et seq.). An understanding of these definitions is important to evaluating the invention because these terms are used to define the claimed subject matter.

The medium of the present invention is provided in a multicompartment assay device with at least three compartments. In one compartment is a medium capable of sustaining the

growth of total microbial organisms (i.e., a control); in a second compartment there is a uropathogen specific medium (which allows for the growth only of the primary urinary gram negative pathogens); and in additional compartments there are provided antimicrobial susceptibility interpretation medium (which contain the uropathogen specific medium with an antimicrobial substance(s) to be evaluated for their effect on the urinary pathogens) (p. 7, line 21 – p. 8, line 26).

The uropathogenic specific medium which is provided in the present invention is specific for the primary gram negative urinary pathogens which include but are not limited to Escherichia coli, Klebsiella spp., Enterobacter spp. and Proteus mirabilis. The primary gram negative urinary pathogens are defined in the specification as those bacteria which cause at least 85-90% of the human and veterinary urinary tract infections (p. 12 of specification). No other medium is available with these capabilities. The capabilities of this medium make the present invention possible which enables the user to collect a nonsterile sample of urine, place it into the respective wells containing a total growth medium, a uropathogenic specific medium, and the media containing the specific antibiotics to be tested, and incubate the samples to determine 1) whether any primary gram negative urinary pathogens are present, and if so, 2) which antibiotics they will be most susceptible to. It is important to note that, because the present invention provides media selective for the primary gram negative urinary pathogens, it is possible to place non-sterile samples into the medium, and growth will be seen only if there is present a primary gram negative urinary pathogen.

ISSUES

Whether the invention of claims 20-24 is obvious over Johnson in view of Sanders when neither reference nor their inappropriate combination teach or suggest a medium selective for the primary gram negative uropathogens.

Whether the invention of claims 20 and 26 is obvious over Johnson in view of Sanders and further in view of Brocco where neither reference nor their inappropriate combination teach or suggest a medium selective for the primary gram negative uropathogens.

Upon examination of the case it will be seen that neither reference, nor any combination thereof, enable the person of ordinary skill to provide a medium which is selective for the primary gram negative urinary pathogens, i.e., a medium which allows for the growth of the group of bacteria which cause at least 85-90% of the human and veterinary urinary tract infections and for substantially less growth of any other bacteria.

ARGUMENT

I. THE PRESENTLY CLAIMED INVENTION IS NOT OBVIOUS OVER THE REFERENCES CITED BY THE EXAMINER

The Examiner rejected claims 20-25 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of Johnson in view of Sanders (Final Office Action mailed 4/28/99, p. 6) and claims 20 and 26 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of Johnson in view of Sanders, and further in view of Brocco. The Examiner has also made of record U.S. Patent No. 4,925,789 to Edberg asserting that it shows

that a medium selective for gram negative bacteria was known in the art at the time of the invention (Interview Summary mailed 7/2/99).

A. The References Cited By The Examiner

Johnson teaches a device for use in exposing a test sample to a variety of antibiotics and for determining the susceptibility of microorganisms to those antibiotics. The device has multiple growth wells in which concentrations of suitable agents are predeposited and dried and rehydrated with inoculum (Col. 2, lines 27-34). The figures of the Johnson reference provide illustrations of the device. **Johnson does not describe any growth medium whatsoever**. Thus, any medium to be used in the device must be those available in the prior art or otherwise provided by the user.

Brocco discloses methods for assaying for microorganism growth or inhibition in the presence of antibiotic. Brocco does not disclose any selective media at all. In the method of Brocco, it is necessary to use a sterile device and sterile medium which contains a particular antibiotic, and to inoculate it with pure cultures of pre-grown bacteria (Brocco, p. 4, lines 3-11). This is done for the purpose of evaluating the susceptibility of those bacteria to particular antibiotics. **If the medium or device is not sterile, any contaminating bacteria will give a false result because, unlike the present invention, the medium of Brocco are not selective for any bacteria, and therefore many types of bacteria will grow in the medium**. The result can only be correlated to the bacteria tested if the medium was inoculated with a pure culture of that bacteria. **In the present invention, these sterility concerns are unecessary because the medium is selective for the primary gram negative urinary pathogens, i.e., only this class of bacteria will grow in the media**.

Sanders discloses a method of determining antibiotic sensitivity which relies on the presence of certain vital enzymes which are common to all bacteria (Col. 2, lines 11-17). A sample specimen is incubated with a substrate for one of the vital enzymes and an antibiotic whose effectiveness against the microbe is sought to be determined. If the substrate for the vital enzyme is acted upon by the bacteria to produce a detectable product, microbe growth is occurring and the microbe is not susceptible to that antibiotic. **Sanders also does not disclose any selective media and requires that the user utilize a sterile device and medium, and inoculate the medium with a pre-grown culture of pure bacteria. Otherwise, contaminating bacteria may give false results, as explained above.**

Edberg discloses a medium for detecting target microbes in a sample by using an indicator which is the preferred or primary nutrient for the target microbe but cannot be substantially metabolized by any other viable microbes which may be present in the sample along with the target microbe (Col. 3, lines 39-42; Col. 4, lines 36-40). The invention therefore uses an active selector by utilizing an enzyme produced only by the target microbe (Col. 3, lines 25-27). Thus, Edberg discloses a medium selective for target microbes. But it is necessary to identify an enzyme substrate which is specific to the target microbe(s) sought to be detected, and is which not hydrolyzed by non-target microbes, and in some embodiments to select antimicrobial agents which inhibit the growth of any nontarget bacteria which also hydrolyze the substrate (Col. 5, lines 19-20; Col. 6, lines 16-17).

B. The Johnson and Sanders References Cited by the Examiner Fail to Support a prima facie Case of Obviousness Because They Fail to Teach or Suggest a Medium for Detecting the Primary Gram Negative Urinary Pathogens in a Biological Sample

When evaluating a claim for determining obviousness, all limitations of the claim must be evaluated. *In re Gulack*, 217 U.S.P.Q. 401 (Fed. Cir. 1983).

The claims at issue recite a method of detecting the presence of urinary pathogens in a biological sample and of simultaneously determining their susceptibility to specific antimicrobial agents. In order to arrive at the present invention it is necessary to provide a uropathogenic specific medium, i.e., a medium which allows only the growth of the primary gram negative urinary pathogens (p. 12 of specification). The primary gram negative urinary pathogens are defined at p. 10 of the specification as the group of bacteria which cause at least 85-90% of the human and veterinary urinary tract infections. **None of the references cited by the Examiner, nor any combination thereof, teach or suggest a uropathogen specific medium, i.e., one that is selective for the primary gram negative uropathogens, as defined in the present application.**

The Examiner states "It would have been obvious to one of ordinary skill in the art at the time of invention to include the medium of Sanders in the method of Johnson where the motivation would have been to provide a positive control for microorganismal growth, as suggested by Johnson" (Final Office Action mailed 4/28/99, p. 8). **But the Sanders reference simply does not teach any medium specific for uropathogens, or any class of organisms. Sanders teaches only a medium which is designed to support the growth of a wide variety of organisms.** The Applicants point out Column 2, lines 6-30 where Sanders explains that there exist "vital enzymes which are common to all living bacteria." Sanders teaches in this section that "a rapid and reliable antibiotic sensitivity detector may be prepared by selecting a substrate

which reacts with a vital enzyme" and that the substrate should be "impregnated into an inert support material along with a nutrient medium and selected antibiotic." The objective is thus to have a medium which allows the growth of all bacteria. Then, antibiotics can be added to the medium to determine the organisms' susceptibility (Col. 4, Chart I). Completely absent from Sanders is any teaching or suggestion of a medium which is capable of selecting for the primary gram negative urinary pathogens, or any particular group of organisms, as is provided and claimed in the present application. The Applicants also point out that Sanders requires that the user utilize a sterile device and medium, and inoculate the medium with a pre-grown culture of pure bacteria (e.g., Col. 5, Chart II; Col. 5, lines 24-25). Otherwise, contaminating bacteria may give false results.

As a matter of law, if each and every element of the claimed invention is not taught or suggested by the prior art, a *prima facie* case of obviousness has not been established. *In re Royka*, 490 F.2d 981, 985; 180 U.S.P.Q. 580 (C.C.P.A. 1974); MPEP § 2142. For the reasons stated, a prima facie case for obviousness has not and cannot be established using the combination of references cited by the Examiner and relief from the rejection is requested.

C. Adding Brocco to the Combination of References Above Does Not Cure the Inappropriateness of the Rejection

This rejection adds the Brocco reference to the combination. The Examiner finds that "Brocco teaches a method of determining susceptibility of uropathogens, specifically Staphylococcus and Streptococcus, to amoxicillin.""(Final Office Action, mailed 4/28/99, p. 9). But as previously pointed out by the Applicants (Response mailed June 3, 1999, p. 5; Response mailed 2/8/98, p. 12) Staphylococcus and Streptococcus are gram positive bacteria and are

clearly not within the scope of the present claims which recite a medium specific for the primary gram negative urinary pathogens. Brocco in no way assists in providing a prima facie case for obviousness since it also fails to teach or suggest a uropathogen specific medium (which selects for the primary gram negative uropathogens). **In fact, Brocco does not provide a medium specific for any organism. The organisms must necessarily be pre-grown, and added to the test medium as pure cultures. This is apparent from reading Example 1** (p. 4, line 32 et seq.; also see p. 4, lines 3-11 directing the use of sterile containers) of Brocco which directs the user to transfer "10 ul of gram negative bacteria" and "200 ul of gram positive bacteria." (p. 5, lines 14-15) which can be obtained only by pre-growing them. The samples are then incubated with these pre-grown, pure cultures and the results read. Conversely, in the present invention, the user collects a sample of urine from, for example, the animal patient which is likely to be contaminated with environmental bacteria (because the urine will be collected with a non-sterile technique and is prone to run along the animal body or fur being contaminated with environmental bacteria before actually being collected) and placed into the medium. **In the present invention, it does not matter that the sample is not sterile in using the present invention because the medium is uropathogenic specific, i.e., allows only for the growth of the primary gram negative urinary pathogens** (pp. 10 and 12 of specification define these terms). Thus, contaminating bacteria which are not primary gram negative urinary pathogens will simply not be seen because they cannot grow in the presently claimed medium which is specific for the primary gram negative urinary pathogens.

D. Adding Edberg to the Combination of References Above Does Not Cure the Inappropriateness of the Rejection

In the Interview Summary mailed 7/2/99, the Examiner included the Edberg reference and stated that it was being supplied to show that a medium selective for gram negative bacteria was known in the prior art at the time of the invention, as were methods of using such a medium for detecting microorganisms. The Applicants do not dispute this point, but point out that it is irrelevant since the claims do not recite detecting gram negative bacteria, but rather detecting the primary gram negative urinary pathogens. The fact that these are also gram negative bacteria in no way implies that by merely detecting gram negative bacteria the invention is obvious. One must, at a minimum, undertake the further experimentation and inventive work of finding a way of screening out all gram negative bacteria other than the primary gram negative urinary pathogens. It was explained in the Third Response After Final (filed 10/14/99, pp. 3-4) that **the medium of the present invention selects against many gram negative bacteria which are not primary gram negative uropathogens**. For example, Bacteriodes, Legionella, Campylobacter, Helicobacter, or Neisseiria are all gram negative bacteria which will not grow in the media of the present invention. This is an important feature since some of these bacteria may find their way into a urine sample by contamination from environmental sources. This is likely to happen particularly in the veterinary context where samples must be collected from an unwilling animal patient, resulting in the urine sample running along the animal's fur and becoming contaminated before collection. The medium of the present invention allows the sample to be collected and tested in a non-sterile environment without adverse results because contaminating bacteria will not grow in the medium of the present invention. Using the teachings of this invention, only the primary gram negative urinary pathogens will grow. The present invention teaches for the first

time a particular combination of antibiotics, nutrients, and other media ingredients which select against all bacteria except the clinically important class of the primary gram negative urinary pathogens. This combination of antibiotics and other medium ingredients is not taught or suggested by any prior art reference. There also do not exist other medium with these capabilities.

Furthermore, Edberg is based on the utilization of an enzyme which is specific to the bacteria or class of bacteria sought to be detected (the "target bacteria"). This enzyme specific to the target bacteria enables them to metabolize a 'nutrient indicator' which, when metabolized, produces a detectable signal (Col. 3, lines 29-32). The nutrient indicator also should be the preferred or primary nutrient source for the microbe (Col. 3, lines 37-39; Col. 4, lines 37-40 and 43-46). For example, in one embodiment at Col. 5, lines 19 et seq. Edberg explains the detection of E. coli, first by adding antibiotics to select against all but gram negative bacteria (lines 29-32). At that point, E. coli are detected when the enzyme β-glucuronidase in E. coli hydrolyzes the nutrient indicator to release a signal. Therefore, nutrient indicators which can be hydrolyzed only by bacteria producing β-glucuronidase are utilized. Of the bacteria remaining in the medium, this enzyme is produced only by E. coli. Similarly, for the detection of Streptococcus (Col. 6, lines 13 et seq.) a nutrient indicator which is a substrate of L-pyronidonyl aminopeptidase is selected since this enzyme is particular to Streptococcus.

Therefore, the detection system of Edberg utilizes the presence of an enzyme in the target bacteria which is not produced by the remaining non-target bacteria. But no such enzyme is known for the class of the primary gram negative urinary pathogens. Thus, the method of Edberg can not be used to arrive at the presently claimed invention.

Furthermore, Edberg also fails to teach any combination of selective agents which selects for the primary gram negative uropathogens. As was explained in the Response mailed 2/8/99, page 8-9, **a combination of medium ingredients and selective agents which selects for the primary gram negative uropathogens is by no means obvious as different combinations of antibiotics interact with each other and with other analytes in the medium to exert differing and often unpredictable effects on cells growing in the medium. In some cases, these interactions will confer increased resistance to certain antibiotics on the part of the target organism. In other cases, the analytes may combine to confer increases susceptibility.** Organisms susceptible to a particular antibiotic in some media may not be susceptible in others. Small changes in medium components can effect substantial changes in resistance patterns. Therefore, the elucidation of a medium containing multiple antibiotics which selects for multiple organisms as the medium of the present invention is not obvious.

As a matter of law, if each and every element of the claimed invention is not taught or suggested by the prior art, a *prima facie* case of obviousness has not been established. *In re Royka*, 490 F.2d 981, 985; 180 U.S.P.Q. 580 (C.C.P.A. 1974); MPEP § 2142. A proper analysis under § 103 requires consideration of whether the prior art would have suggested to one of ordinary skill in the art to carry out the claimed process, and whether the prior art would have revealed that in doing so, one of ordinary skill in the art would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.* The prior art does not teach or suggest what ingredients must be combined or what principle to follow to arrive at a uropathogen specific medium as is claimed, i.e., a medium which allows for the growth of the primary gram negative urinary pathogens, and for

substantially less growth of any other bacteria (see definition, p. 12 of specification). **The present application teaches such a medium quite specifically at page 19.**

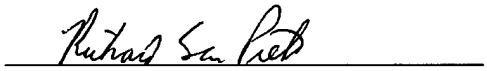
Relying on the prior art references cited by the Examiner, the person of ordinary skill does not find the teachings to arrive at a medium which allows only for the growth of the primary gram negative urinary pathogens. Furthermore, the prior art does not indicate it is even possible to arrive at a medium which is selective for this class of bacteria. This concept is taught only by the present application. But the law does not allow an obviousness determination which is arrived at through the use of hindsight where that which only the inventor taught is used against its teacher. *W.L. Gore Assoc. Inc., v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983).

For the foregoing reasons, a prima facie case of obviousness is not established over the references cited by the Examiner and relief from the rejection is sought.

CONCLUSION

In view of the above discussion, Applicant submits that claims 115-134 are allowable. Applicant respectfully requests that they be allowed and passed to issue.

Respectfully submitted,



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APPENDIX

20. A method of detecting the presence of urinary pathogens in a biological sample and of simultaneously determining the susceptibility of the urinary pathogens to antimicrobial agents, said method comprising:

providing a multicompartment assay device comprising:

at least one compartment comprising a medium capable of sustaining growth of total microbial organisms; at least one compartment comprising a uropathogenic specific medium; and, at least one compartment comprising an antimicrobial susceptibility interpretation medium;

placing a portion of the biological sample respectively in said at least one compartment comprising a medium capable of sustaining growth of total microbial organisms; said at least one compartment comprising a uropathogenic specific medium; and, said at least one compartment comprising an antimicrobial susceptibility interpretation medium comprising an antimicrobial agent;

whereby growth of organisms in said at least one compartment comprising a medium capable of sustaining growth of total microbial organisms indicates the presence of microbial organisms in the sample; growth of organisms in said at least one compartment comprising a uropathogenic specific medium indicates the presence of urinary pathogens in the sample, and growth of organisms in said at least one compartment comprising an antimicrobial susceptibility interpretation medium indicates that the organisms lack susceptibility to the antimicrobial agent comprised in said antimicrobial susceptibility interpretation medium; and

examining the compartments to determine the presence of urinary pathogens in said biological sample and the susceptibility of said urinary pathogens to said antimicrobial agents.

21. The method of claim 20, wherein the biological fluid is urine.

22. The method of claim 21, wherein the urinary pathogens are primary gram negative urinary pathogens.

23. The method of claim 22 wherein the primary gram negative urinary pathogens comprise *Enterobacteriacae*.

24. The method of claim 22 wherein the primary gram negative urinary pathogens are selected from the group consisting of: *Escherichia coli*, *Klebsiella spp.*, *Enterobacter spp.*, *Proteus mirabilis, Proteus vulgaris, Morganella morganii, Providencia retteri*, and *Acinetobacter spp.*

26. The method of claim 20 wherein the at least one antimicrobial susceptibility interpretation medium comprises amoxicillin, clavulanic acid/amoxicillin, or enrofloxacin.